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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,290	VOLLMERS ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *72-91 and 95-116* is/are pending in the application.

4a) Of the above claim(s) *89,90 and 95-97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *72-79, 82-88 and 98-116* is/are rejected.

7)☒ Claim(s) *80 and 81* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/17/09* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 72-91 and 95-116 are all the pending claims for this application.

2. Claims 72, 73, 75, 77 and 108 were amended in the Response of 2/17/09.

3. Claims 89-90 and 95-97 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in the reply filed on 6/2/08.

4. Claims 72-88 and 98-116 are all the pending claims under examination.

5. Applicants amendments to the claims have necessitated new grounds for rejection. This action is FINAL.

Information Disclosure Statement

6. The IDS of 2/17/09 has been considered and entered. The reference for which an incomplete copy was provided has been stricken on the 1449 form. Otherwise an examiner's initialed and signed copy of the 1449 form for those reference considered is attached.

7. The information disclosure statements filed 11/17/08 and 2/11/09 fail to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) *a*

column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered.

Withdrawal of Objections

Specification

8. The objections to the specification for the following informalities are withdrawn:

a) The specification has been *properly* amended to cross-reference the related priority applications in the Response of 2/17/09.

b) The trademarks, e.g., Cytoxan®, have been amended to properly identify the trademark in the Response of 2/17/09.

Claim Objections

9. The objections to Claims 72 and 75 for the following informalities are withdrawn:

a) The second occurrence of the duplicate phrase “an adenocarcinoma of the esophagus” has been deleted for both Claims 72 and 75;

b) The typographical error in Claim 75 for phrase "a diffuso-type gastric carcinoma" has been corrected to “diffuse-type”.

Objections Maintained

Specification

10. The objection to the figure legend to Figures 10A and 10B for failing to describe the x- and y-axis labels for each of the panels is maintained.

Applicants allege on p. 12 of the Response of 2/17/09 “In terms of the objection to Figures 10A and 10B for allegedly not describing the x- axis or y-axis, in view of the description of Figure 10A and 10B set forth on page 27, lines 16-25, the x-axis of 10A and 10B refer to tumor weight and tumor volume, respectively. As to the y-axis, in view of the description of Figure 10A and 10B it appears that this axis represents a particular mouse.”

Response to Arguments

Closer inspection of both Figure 10A and 10B reveals that both the SAM-6 sample and control are both designated by the same “open” circle which does not permit the viewer to discern the effects of SAM-6 from the control in either panel. Further, it is still unclear how each of the test and control samples relates to the

"particular mouse" on the y-axis and the corresponding "tumor weight and tumor volume, respectively" on the x-axis. Finally, it is not clear to the examiner how the y-axis can be particular mouse, especially for panel A where the scale appears in increasing 0.05 increments. This is the same for panel B where the scale increases by hundredth increments.

If Applicants can correct this error or omission without filing a new figure they are welcome to amend the specification. In this case, they are advised to carefully check the specification for original support in order to avoid a new matter issue.

Applicants are also requested to carefully check the other figures in the specification for similar inconsistencies (see for example, Figure 8) and which might be addressed by amending the specification.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

11. The rejection of Claims 72-79, 82-88 and 98-116 under 35 U.S.C. 112, first paragraph, is maintained because the specification does not reasonably provide enablement for any anti-GRP78^{SAM-6} antibody having: at least 75%, 80%, 85%, 90% or 95% identity to either the VL of SEQ ID NO:1 and/or the VH of SEQ ID NO:3, or a single

VL domain (SEQ ID NO:1) or a single VH domain (SEQ ID NO:3), or a single CDR domain or less than the full complement of VL CDR1-3 and VH CDR1-3.

For purposes of review, the rejection was set forth in the Office Action of 9/19/08 as follows:

"Nature of the Invention/ Skill in the Art

The claims are interpreted as broadly encompassing of an antibody or antigen binding fragment thereof with binding specificity for the antigen expressed on an adenocarcinoma of the lung, squamous cell lung carcinoma, intestinal type gastric carcinoma, diffuse type gastric carcinoma, adenocarcinoma of the colon, adenocarcinoma of the prostate, squamous cell carcinoma of the esophagus, adenocarcinoma of the esophagus, lobular carcinoma of the breast, ductal carcinoma of the breast, adenocarcinoma of the pancreas, adenocarcinoma of the ovary, and adenocarcinoma of the uterus, or that it binds to the following cell lines: BXPC-3, 23132/87, COLO-206F, COL0-699 or LOU-NH91, and where the antibody has: at least 75%, 80%, 85%, 90% or 95% identity to either the VL of SEQ ID NO:1 and/or the VH of SEQ ID NO:3, or a single VL domain (SEQ ID NO:1) or a single VH domain (SEQ ID NO:3), or a single CDR domain or less than the full complement of VL CDR1-3 and VH CDR1-3 from SEQ ID NO:1 and/or SEQ ID NO:3.

The relative skill in the art required to practice the invention is a molecular immunologist.

Disclosure in the Specification

The specification generally contemplates making antibodies on p. 29, line 16 to p. 34, line 21; generating antibody variants by DNA modifications on p. 34, line 23 to p. 36, line 26. The specification provides definitions for functional antibody fragments (p. 14, lines 14-25).

The specification discloses a single isolated antibody, SAM-6, selected from a library of antibodies generated by fusing lymphocytes from a human stomach adenocarcinoma patient (Table 1) with the heteromyeloma cell line HAB-1 to produce a trioma. At the time of filing, Applicants specification did not reveal the identity of the antigen but generally characterized the antigen immunohistochemical screening of SAM-6 against normal tissues and autologous tumor where the antigen was defined by the cancer cell-binding properties for the antibody (Example 2). SAM-6 showed no reactivity with normal tissues but different tumor tissues (Tables 3 and 4). Partial characterization of the antigen in Example 3 showed by Western blot analysis the antibody recognized proteins of 140 kDa (Figure 3A). Rauschert et al (Lab. Invest. 88:375-386 (2008)) later described the antigen as GRP78 and the epitope is an O-linked carbohydrate moiety. The sequence for SAM-6 was determined for VL and VH (Example 2). Sam-6 antibody was shown to induce apoptosis in the cell lines BXPC-3 and 23132/87 (Example 4); and inhibit proliferation of the cell line 23132/87 (Example 5).

The specification contemplates but does not specifically disclose working embodiments for just any of the antibody structures encompassed by the claims much less that any modified antibody would have the required properties of recognizing an adenocarcinoma of the lung, squamous cell lung carcinoma, intestinal type gastric carcinoma, diffuse type gastric carcinoma, adenocarcinoma of the colon, adenocarcinoma of the prostate, squamous cell carcinoma of the esophagus, adenocarcinoma of the esophagus, lobular carcinoma of the breast, ductal carcinoma of the breast, adenocarcinoma of the pancreas, adenocarcinoma of the ovary, and adenocarcinoma of the uterus, or that it binds to the following deposited cell lines: BXPC-3, 23132/87, COLO-206F, COL0-699 or LOU-NH91.

Without sufficient guidance in the written description alone, the ordinary artisan could not practice making and using the myriad antibody embodiments encompassed by the claims because the specification and claims do not define which regions and domains are subject to variation, which regions or domains could tolerate the introduction of the variation, or the nature and extent of the variation. For example, the claims are not limited to whether the extent of variation comprises amino acid substitutions, insertions, deletions and combinations thereof so that the ordinary artisan could predict which variation would not compromise antigen binding specificity. The claims are not limited as to whether the variation occurs in the antigen binding domains or Fc regions, or the CDRs and/or framework domains. Thus it is not readily apparent from the specification or the original claims as filed, how the ordinary artisan could practice the invention without incurring undue experimentation in order to identify a reasonable number of working embodiments based on the extent of antibody variation encompassed by the claims. Further, the claims encompass antibody embodiments having structures that are generally viewed in the field of art as being non-

operative or at least unpredictable as to their antigen affininty, namely, antibodies having single variable domains or those having fewer than the full complement of both VL and VH CDRs. Thus the ordinary artisan could not reduce to practice the myriad embodiments and expect to obtain a reasonable number of working embodiments absent undue experimentation at the levels of gene manipulation, antibody screening and bioassay performance.

Prior Art Status: Single CDR-domain Antibodies

The claims encompass isolated antibodies comprising a single CDR domain (and less than the full complement of VH/VL CDRs) from SAM-6 antibody. Applicants have not shown that any isolated any antibody comprising less than a full complement of VH/VL CDRs from a parent SAM-6 antibody would retain the antigen binding to any on the cell lines test in the assays. In fact there are numerous publications acknowledging that the conformation of CDRs as well as framework residues influence binding.

MacCallum *et al.* (J. Mol. Biol. 262:732-745 (1996)) analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.).

de Pascalis *et al.* (Journal of Immunology 169, 3076-3084 (2002)) demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right col.). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left col.).

The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset *et al.* (BBRC 307, 198-205, (2003)) which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset *et al.* also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and a framework residue located just before the H3 (see page 202, left col.).

Vajdos *et al.* (J. Mol. Biol. 320, 415-428 (2002)) additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left col.).

Holm *et al* (Mol. Immunol. 44: 1075-1084 (2007)) describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were involved in antigen binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract).

Chen *et al.* (J. Mol. Bio. 293, 865-881 (1999)) describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866).

Wu *et al.* (J. Mol. Biol. 294, 151-162 (1999)) state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation.

Thus, while one can make the statement that a single CDR makes a significant contribution in the antigen binding, the residues in these CDRs are not the only residues that influence binding and in fact the prior art as well as applicants own disclosure do not support that it was clearly established, that the a single CDR domain alone is sufficient to define the binding specificity of an antibody, and that multiple antibodies can predictably be generated having the same binding specificity based on a single CDR (or less than full complement of VH CDRs and VL CDRs).

Analyzing applicants own disclosure, which while it does contemplates divergent CDR residues, the only working example is the SAM-6 antibody having heavy chain CDRs paired with complementary light chain CDRs. Additionally, the data indicate that it is the frameworks and CDRs that contribute to antigen binding. Further, there are no examples of mixing or matching of the light chain CDRs or heavy chain CDRs and most importantly there is no working example of placing a single CDR domain of a heavy chain and/or a light chain in just any framework and producing an antibody that binds antigen as broadly claimed or suggested.

Prior Art Status: Conservative Amino Acid Substitutions within CDR/FR Residues

The claims encompass antibodies comprising VH domains, VL domains and CRDs which vary in the extent to which they resemble the corresponding domain in the parent SAM-6 antibody. This variation can comprise any number and kind of amino acid substitutions. It is not well established in the art that all variable domains are amenable to modifications much less that that substitutions are for conservative amino acids. Numerous publications acknowledge that conservative substitutions would in fact change the binding ability of antibodies if not substantially reduce the affinity.

Brummell *et al.* (Biochemistry 32:1180-1187 (1993)) found that mutagenesis of the four HCDR3 contact residues for the carbohydrate antibody (Salmomella B O-polysaccharide) in no instance improved affinity but 60% of the mutants resulted in a 10-fold drop in binding constant (affinity electrophoresis value of 0.85), while still other mutants were lower (Table 1 and p. 1183, Col. 2, ¶2 to p. 1184, Col. 1, ¶1). Brummell demonstrates that no substitution retained antigen binding affinity similar to the wild type antibody despite targeted, conservative substitutions in known contact sites.

Kobayashi *et al.* (Protein Engineering 12:879-844 (1999)) discloses that a scFv for binding a DNA oligomer containing a (6-4) photoproduct with Phe or Tyr substitutions at Trp 33 retained "a large fraction of the wild-type binding affinity, while the Ala substitution diminished antigen binding" (Table 1). However, Kobayashi notes "replacing Trp 33 with Phe or Ala alters the local environment of the (6-4) photodimer since binding is accompanied by large fluorescence increases that are not seen with the wild-type scFv" (p. 883, Col. 2, ¶3).

Burks *et al.* (PNAS 94:412-417 (1997)) discloses scanning saturation mutagenesis of the anti-digoxin scFv (26-10) which also binds digitoxin and digoxigenin with high affinity and with 42-fold lower affinity to ouabain. 114 mutant scFvs were characterized for their affinities for digoxin, digitonin, digoxignenin and oubain. Histogram analysis of the mutants (Figure 2) reveals that "not all residues are optimized in even high affinity antibodies such as 26-10, and that the absence of close contact with the hapten confers higher plasticity, i.e., the ability to tolerate a wider range of substitutions without compromising binding (p. 415, Col. 2, ¶4- p. 416, ¶1).

Brummell *et al.*, Kobayashi *et al.* and Burks *et al.* introduced conservative amino acid substitutions into CDRs to examine binding effects and demonstrate that any conservative substitution within any CDR cannot be made without affecting binding.

Jang *et al.* (Molec. Immunol. 35:1207-1217 (1998)) teach that single amino acid mutations to the CDRH3 of a scFV derived from 2C10, an anti-dsDNA autoantibody, reduced the binding activity about 20-50% compared to the unmutated scFv (Table 4).

Brorson *et al.* (J. Immunol. 163:6694-6701 (1999)) teach that single amino acid substitutions to the CDRs of IgM Abs for the bacterial protein, levan, are ablated.

Coleman (Research in Immunol. 145:33-36 (1994)) teaches that single amino acid changes within the interface of an antibody-antigen complex are important and that inasmuch as the interaction can tolerate amino acid sequence substitutions, "a very conservative substitution may abolish binding" while "in another, a non-conservative substitution may have very little effect on the binding" (p. 35, Col. 1, ¶1).

Prior Art Status for Single Variable Domain Antibodies

Smith-Gill et al. (J. Immunol. 139:4135-4144 (1987)) observed from chain recombination experiments that through interactions between the VH/VL pair, specificity for antigen is H chain determined, specific binding is increased when L chains of the same parental isotype are used, and that both H and L chains determine fine specificity.

Kumar et al. (J. Biol. Chem. 275:35129-35136 (2000)) discloses Fab molecules with anti-DNA (light chain) and anti-cardiolipin (heavy chain) binding activities, and that pairing of the partner chains is dependent on the particular H/L chain pairing.

Song et al. (Biochem Biophys Res Comm 268:390-394 (2000)) discloses that affinity and specificity of scFv for preS1 protein of HBV is dependent on S-S bond formation in conferring correct refolding of the fragments for retaining binding properties, and that L chains are predominant in antigen binding.

Therefore, selecting and producing just any variable domain substituted antibody with the ability to properly associate and assemble into a fully functional antibody which maintains the binding specificity for the original antigen would be highly unpredictable based on the methods described in the specification and the prior art disclosures.

Unpredictability/Undue Experimentation

The specification provides no direction or guidance regarding how to produce the genus of antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Furthermore, while the level of skill required to generate the antibodies is that of a molecular immunologist, the ordinary artisan would have been required to identify candidate amino acid residues for substitution in the FR and/or CDR domains, perform the mutagenesis on the FR and CDR domains, produce and express the modified antibodies, measure binding characteristics (e.g., binding specificity, equilibrium dissociation constant (K_D), dissociation and association rates (K_{off} and K_{on} respectively), and binding affinity and/or avidity compared with the parent antibody) in a BIAcore assay, and then finally perform bioassays to identify any one or more of the characteristics of the antibody. The technology to perform these experiments was available at the time of application filing, but the amount of experimentation required to generate even a single FR- and/or CDR-modified antibody meeting all of the claim limitations would not have been routine much less could one of ordinary skill in the art predict that any one or combination of all the FR and CDR amino acid

substitutions encompassed by the claims would result in *just any* substituted antibody clone having retained the antigen binding activity (MPEP 2164.06, "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (In re Wands, 858 F.2d 731, 737, 8 USQP2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

Applicants' allegations on pp. 12-17 of the Response of 2/17/09 have been considered and are not found persuasive.

A) Applicants allege "there is no need for the skilled artisan to "predict which variation would not compromise antigen binding specificity" in advance in order to make variants and functional fragments because making variant antibodies and functional fragments and screening to determine those with binding activity was routine and well established at the time of the invention."

Boder et al. (Proc. Nat'l Acad. Sci. USA 97:10701 (2000) Exhibit A) describes directed evolution of scFv fragments using the method developed by Stemmer W. P., Nature 370:389 (1994). A large number of Fv sequences had improved binding affinity, with a dissociation rate greater than 1000 fold slower than the native non- mutagenized antibody (see, abstract).

Response to Arguments

The specification and the prior art reference does not identify 1) a complete structure, ii) partial structure, iii) physical and/or chemical properties, or iv) functional characteristics coupled with correlation between *structure and function* for the genus of antibodies that a) bind the same epitope as the SAM-6 antibody, b) inhibits cell proliferation of 23132/87 (DSMZ Accession No. ACC 201) cells and c) induces apoptosis of at least one of BXPC-3 (ATCC Accession No. CRL- 1687) and 23132/87

(DSMZ Accession No. ACC 201) cells (see MPEP 2105 and Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406).

B) Applicants allege "An antibody, by definition, includes three CDRs in at least a heavy chain variable region sequence. Consequently, as the claims are directed to antibodies that bind to an epitope of an antigen, which include 3 CDRs on the heavy chain variable region sequence, the ground for rejection relating to a single CDR is not relevant."

Response to Arguments

Applicants attention is drawn to pending Claims 86 and 111, each of which recite "wherein the antibody of antibody fragment includes *at least one* complementary-determining region (CDR)...". The phrase "at least one" is interpreted as there being only a single CDR domain from the VH and VL domain. Further, Claims 82-85, 102, 103, 109 and 110 are interpreted as being drawn to single variable domain antibodies, which as asserted in the previous Office Action are art-recognized as being unpredictable in binding properties.

It is noted that the features upon which applicant relies (i.e., An antibody includes three CDRs in at least a heavy chain variable region sequence) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

C) Applicants allege "In terms of the publications cited at pages 12-14 of the Action as evidence that conservative amino acid substitutions in the CDR/FR residues

"change binding ability of antibodies if not substantially reduce the affinity," Applicants respectfully point out that the claims do not recite a particular binding affinity. Consequently, even if a change were to increase or decrease affinity for the epitope of the antigen expressed by at least one of the recited cells types, that antibody is included, provided binding is detectable by an assay."

To corroborate that substitutions within CDRs are tolerated, submitted Kipriyanov et al. (Protein Engineering 10:445 (1997)) report that a substitution of a cysteine residue by a serine within CDR3 of an antibody heavy chain variable region did not have an adverse effect on affinity.

To corroborate that substitutions within FRs are tolerated, Holmes et al. (J. Immunol. 167:296 (2001)) report several heavy chain variable region FR substitutions of an anti-lysozyme antibody did not destroy binding activity.

To corroborate that insertions and deletions of amino acid residues in heavy and light chain variable regions, including CDRs, are tolerated submitted Wilson et al. (J. Exp. Med. 187:59 (1998)) report a number of insertions and deletions of variable heavy chains that occur naturally during affinity maturation which are tolerated.

To further corroborate that insertions and deletions of amino acid residues in heavy and light chain variable regions, including CDRs, are tolerated Lantto and Ohlin (J. Biol. Chem. 277:45108 (2002)) report that single amino acid insertions or deletions of CDRs 1 and 2 of heavy chain variable region of an antibody were well tolerated.

Response to Arguments

The examiner appreciates the individual examples of modified antibody species that are taught in each of the references, where the modifications were specifically described and targeted for certain domains and residues. However, none of the instant claimed modifications are in any way described insofar as whether they occur in the CDR and/or framework domains, the kind of modifications, the residues effected by the modification, or those residues that are required as being essential for binding, etc. The claims encompass antibodies comprising a percent variation between the antibody VH/VL and/or CDR and/ or framework with respect to the VL and VH of SEQ ID NOS: 1 and 3, without providing a structure function correlation between the antibody sequence comprising the modifications and the function of the antibody. The claims encompass not only antibodies that are required to bind the epitope of the SAM-6 antibody but to have a functional, biological effect.

Applicants have not established by a preponderance of the evidence the structure/function correlation for the claimed antibodies that would enable the ordinary artisan to predict making and using the broad scope of antibodies with a reasonable degree of certainty absent further experimentation (See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species

when … the evidence indicates ordinary artisans *could not predict the operability in the invention* of any species other than the one disclosed.").

The rejection is maintained.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

12. Claims 72-79, 82-88 and 98-116 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 72-79, 82-88 and 98-116 are *interpreted* as being drawn to any antibody that binds the same epitope as the SAM-6 antibody, but which epitope occurs on any number of antigens expressed on the list of neoplastic cells in Claims 72-74 and which antibody may be merely cross-reactive with the SAM-6 epitope. It is the examiner's position that the only antigenic epitope disclosed in the specification as being expressed by the neoplastic cells and recognized by the SAM-6 antibody, is the O-linked

carbohydrate moiety on a post-transcriptionally modified isoform of the 78-kDa GRP, designated $GRP78^{SAM-6}$.

Under the Written Description Guidelines (66 FR 1099 (Jan. 5, 2001); 1242 O.G. 168 (Jan. 30, 2001) revised training materials Mar 28, 2008), the claimed invention must meet the following criteria as set forth.

a) Actual reduction to practice: the specification did not reveal the identity of the antigen but generally characterized the antigen by immunohistochemical screening of SAM-6 against normal tissues and autologous tumor where the antigen was defined by the cancer cell-binding properties for the antibody (Example 2). SAM-6 showed no reactivity with normal tissues but different tumor tissues (Tables 3 and 4). Partial characterization of the antigen in Example 3 showed by Western blot analysis the antibody recognized proteins of 140 kDa (Figure 3A). Rauschert et al (Lab. Invest. 88:375-386 (2008); cited in the PTO 892 form of 9/19/08) later described the antigen as GRP78 and the epitope is an O-linked carbohydrate moiety.

b) Disclosure of drawings or structural chemical formulas: the specification and drawings do not show that applicant was in possession of the epitope on any antigen other than the $GRP78^{SAM-6}$ protein and to which the SAM-6 antibody binds.

c) Sufficient relevant identifying characteristics: the specification does not identify 1) a complete structure, ii) partial structure, iii) physical and/or chemical properties, or iv) functional characteristics coupled with correlation between structure and function for the epitope for the genus antigens against which any antibody could be generated and to which SAM-6 antibody binds.

d) Method of making the claimed invention: the specification teaches making and screening antibodies and selecting the SAM-6 antibody, where as evidenced by Rauschert et al (Lab. Invest. 88:375-386 (2008); cited in the PTO 892 form of 9/19/08), the antigen was identified as GRP78 and the epitope is an O-linked carbohydrate moiety.

e) Level of skill and knowledge in the art: The term “specific” binding is not an absolute, in other words, the claimed antibody is not excluded from being cross-reactive for binding the same epitope also recognized by the SAM-6 antibody. It is noted that the term “specific binding” is not used in the immunological arts to connote exclusive binding. “Specifically binds” is not art-defined as exclusive binding as evidenced by Bost et al. (Immunol. Invest. (1988) 17:577-586) and Bendayan (J. Histochem. Cytochem. (1995) 43:881-886). That an antibody "cross-reacts", i.e., binds to more than one protein sequence, does not mean that the antibody does not "specifically react" or "specifically bind" with both proteins. For example, Bost et al. describe antibodies which "cross-react" with IL-2 and HIV envelope protein, but establish that the binding of each protein is due to the presence of a homologous sequence in each protein in which 4 of 6 residues were identical (see entire document, but especially the Abstract and Discussion). Antibodies that bound either the HIV or IL-2 derived sequence, did not cross react with irrelevant peptides (e.g., "Results, page 579). Similarly, Bendayan characterizes the specific reactivity of a monoclonal antibody produced to human proinsulin and shows that although the antibody is highly specific; it is nevertheless able to bind to not only human proinsulin, but to proinsulin from other species and even a

distinct protein, glucagon, based upon conservation of an Arg-Arg dipeptide sequence in each of these molecules (see entire document). Bendayan concludes that "an antibody directed against such a sequence, although still yielding specific labeling, could reveal different molecules not related to the original antigen" (page 886, last paragraph). See also USPN 6,210,670 (Berg) “Cross-Reacting Monoclonal Antibodies Specific for E-Selectin and P-selectin". Specificity of antibody interaction with epitopes is defined by particular amino acid sequences. Consequently, it was well known in the art at the time the invention was made that antibody binding of distinct proteins was indeed specific. Applicants have not demonstrated with sufficient evidence the uniqueness or exclusiveness of any antibody recognizing and binding to the epitope on any antigen where the same epitope is recognized by the SAM-6 antibody. .

f) Predictability in the Art: Adequate written description for an antibody appears to hinge upon whether the specification provides adequate written description for the antigen. While a specification may enable making a genus of antibodies, this does not necessarily place applicant in possession of the resultant antibodies (See *In re Kenneth Alonso* October (Fed. Cir. 2008)) sustaining a lack of adequate written description rejection where “the specification teaches nothing about the structure, epitope characterization, binding affinity, specificity, or pharmacological properties common to the large family of antibodies” where the specification does not characterize the antigens to which the monoclonal antibodies must bind).

Applicants have not characterized the epitope occurring on any antigen to which the claimed antibody should specifically and exclusively bind, and therefore, the

ordinary artisan could reasonably conclude that Applicants were in possession of the claimed genus of antibodies.

Conclusion

13. No claims are allowed.

14. The VL (SEQ ID NO:1) and VH (SEQ ID NO:3) domains of the SAM-6 antibody are free from prior art. Claims 80 and 81 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn Bristol/
Examiner, Art Unit 1643
Temporary Full Signatory Authority